Article

Discovery Medicine 2023; 35(174): 73–81
https://doi.org/10.24976/Discov.Med.202335174.8

Clinical Value of Surgery and Establishment a Predictive Model for Breast Cancer Patients with Bone-Only Metastasis

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Published: 1 February 2023

Background: Whether to perform surgery on breast cancer with initial bone metastasis is heatedly debated. The aim of this study was to assess the efficacy of surgery to prolong survival time towards breast cancer patients with bone-only metastasis, and create a prognostic nomogram to predict long-term survival.
Methods: Patients diagnosed with bone-only metastatic breast cancer from 2010 to 2015 were included in this study. National Cancer Database (NCDB) was used to obtain patients' data.
Results: A total of 7751 patients were included for final analysis, among which 3114 (40.2%) patients had received specialized breast surgery and 4637 (59.8%) had not. Patients who had undergone surgery showed a superior overall survival (OS) compared to patients without surgery (multivariate: HR (hazard ratios) = 0.58; 95% CI (confidence interval) [0.54–0.62]; $p < 0.001$). Moreover, survival benefit from surgery was also true in almost all subgroups. Prognostic nomogram to individually predict patients' long-term survival rate exhibited an acceptable predictive capability, with a C-index around 0.7 both in training and validation cohorts. Clinicopathological factors included in the nomogram could discriminate patients into subgroup with different prognoses.
Conclusions: Our data suggests that surgery may enhance OS in patients with initial bone-only metastatic breast cancer. Additionally, the created nomogram showed an acceptable could predict patients' long term survival.

Keywords: breast cancer; bone metastasis; surgery; NCDB; survival

Introduction

Recent epidemiological data showed an increased incidence and mortality in breast cancer patients [1]. Despite a huge improvement in treatment strategies, prognosis remains grim, especially in patients with distant metastasis. Approximately 6% of breast cancer patients have experienced distant metastases at the time of initial diagnosis [2]. Metastatic breast cancer (MBC) patients have a median survival time of 18–24 months, with survival rates as low as 27% and 13% at 5 and 10 years after diagnosis [3].

In recent years, a growing body of literature with retrospective studies suggested a positive impact on patients' survival when removing the primary tumor in metastatic breast cancer [4–7]. The clinical trial named MF07-01 (NCT00557986) in Turkey showed a statistically significant improvement in overall survival in breast cancer patients that underwent surgery, particularly in patients younger than 55 years old, negative human epidermal growth factor receptor 2 (Her2), positive hormone receptors (HR), or solitary bone-only metastases [8]. However, other retrospective and prospective studies in India have failed to demonstrate a positive impact on patients' survival when surgical intervention was performed on metastatic breast cancer patients [9–11]. There is still a lack of agreement among clinicians regarding whether to perform primary tumor surgery on patients with metastatic breast cancer.

It has been reported that approximately 25–40% of patients with metastatic breast cancer have bone metastases as first distant disease site [12]. There are 17–37% of breast cancer patients whose distant diseases are limited to bone [13,14]. Moreover, those patients tended to have better clinical outcomes than those who suffer metastases at other sites [15]. Although bone metastases often result in skeletal related events (pathological fractures, ostealgia, or osteolysis) that reduce quality of life, systematic failure (e.g., respiratory failure, liver failure, or cerebral hernia) is rare [16]. In part, this might explain its better prognosis as well as tolerability for surgery. Hence, it is hypothesized that surgery positively impact survival of breast cancer patients with bone-only metastases. The aim of this study was to compare the clinical outcome of breast cancer patients with bone-only metastases who had received surgical treatment or not.

Methods

Database and Patients Selection

Patients' clinical data were extracted from the National Cancer Database (NCDB) database that represents approximately 70% of newly diagnosed cancer cases in the United States, which is jointly sponsored by the American Cancer Society and the American College of Surgeons. Extracted data included breast cancer patients with bone metastasis who were diagnosed from 2010 to 2015.

Patients were excluded for any of the following reasons: (1) With metastasis other than bone, (2) male patients, (3) not first tumor, (4) lack of information about race, insurance, histological grade, American Joint Committee on Cancer (AJCC) T stage, AJCC N stage, subtype, surgery, radiation, chemotherapy, and hormone therapy. Overall, 7751 eligible patients were included in the study (Fig. 1). Subsequently, patients were 1:1 randomly divided into a training cohort and a validation cohort. Training cohort was used to create a nomogram which effectiveness was verified with the validation cohort.

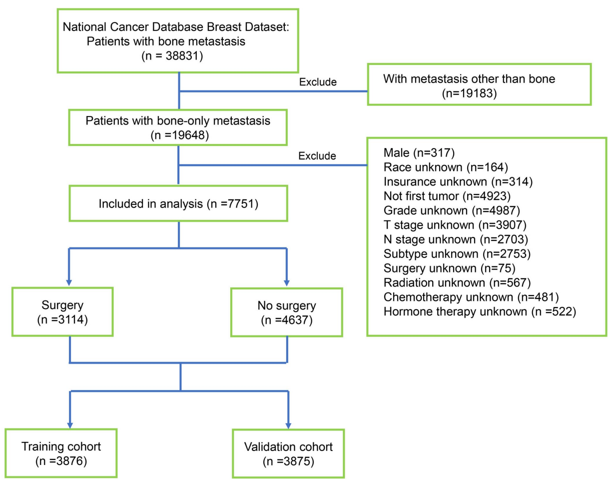

Fig. 1. Patient selection flowchart.

Multiple variables were extracted from the NCDB database including demographics characteristics (age at diagnosis, race, and insurance status), disease characteristics (histological grade, histological subtype, AJCC T, and N stage), and treatment characteristics (surgery, radiotherapy, chemotherapy, and hormone treatment). A categorical variable was created from the continuous variables mentioned before, such as age of diagnosis (<35, 35–49, 50–69, and ≥70). The primary endpoint to assess was overall survival (OS).

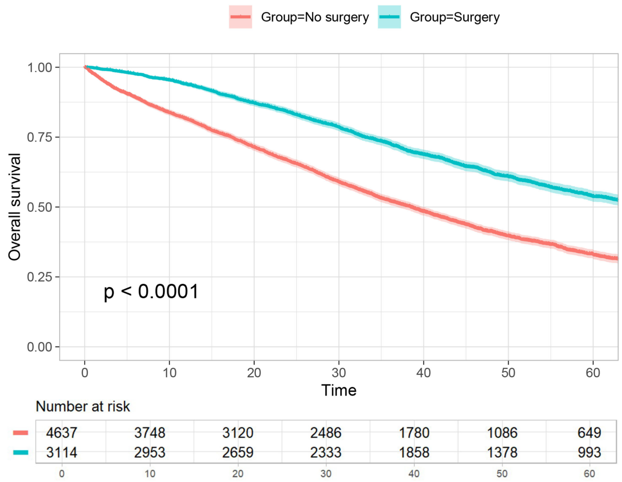

Fig. 2. Kaplan–Meier curve of OS for breast cancer patients with bone-only metastases who underwent surgery or did not. OS, overall survival.

Statistical Analysis

Demographic and clinicopathological factors were summarized using descriptive statistics. Pearson χ^2 test was used to evaluate correlations between clinicopathological factors. Kaplan–Meier survival curves were plotted to assess survival. A 2-sided log-rank test was used to assess survival differences between groups (received surgery or not). Moreover, a univariate and multivariate Cox regression analysis were performed to calculate hazard ratios (HR) with 95% confidence interval (CI). Additionally, nomograms were developed to predict OS (overall survival) in 1-, 3- and 5-years. An estimation of the consistency between the observed outcomes and the predictions based on the nomogram was performed by plotting calibration curves.

Descriptive statistics, Pearson χ^2 test, Cox proportional hazards model, and logistic regression model were calculated using SPSS 24.0 (IBM Corp, Armonk, NY, USA). Kaplan–Meier analysis was performed using R software (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria). Nomogram was created using R package "rms" and "survival". A 2-sided p-value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 7751 patients were included for the final analysis, among which 3114 (40.2%) patients had received specialized breast surgery and 4637 (59.8%) not. Patients' clinicopathological information is presented in Table 1. Pa-

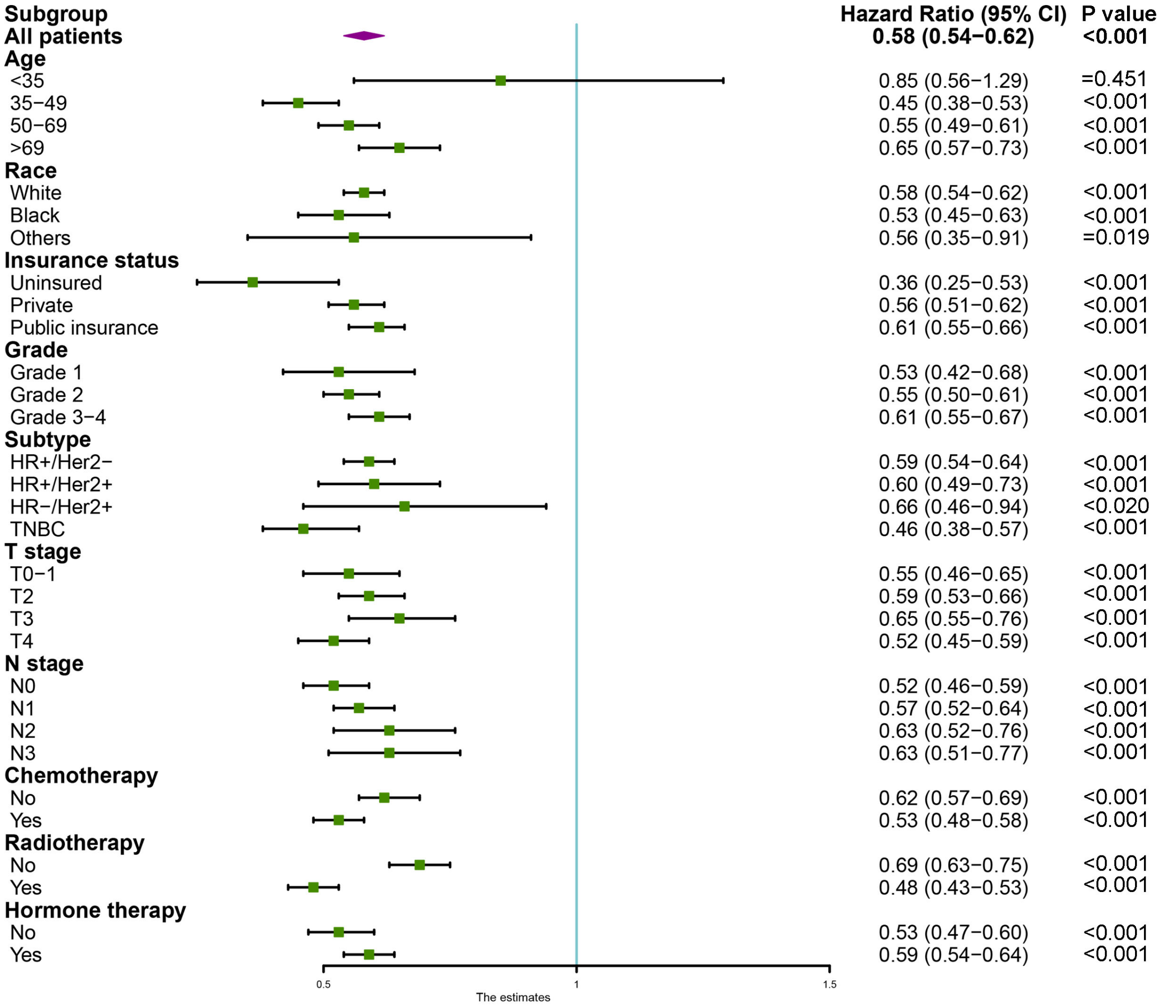

Fig. 3. Multivariable Cox regression analysis of OS for breast cancer patients with bone-only metastases. Analysis performed in all patients and subgroups.

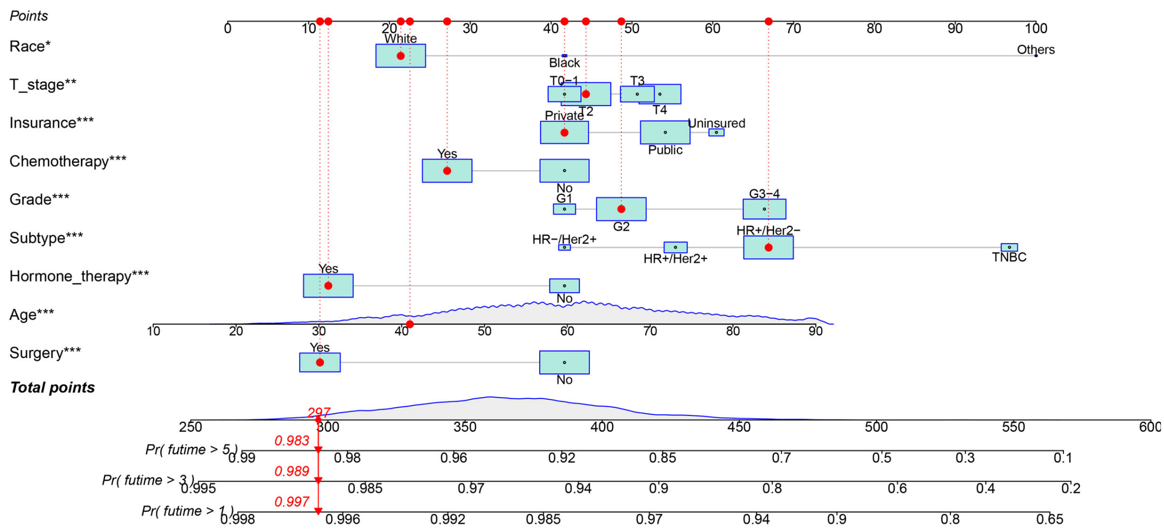

Fig. 4. Nomogram predicting the OS probability. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

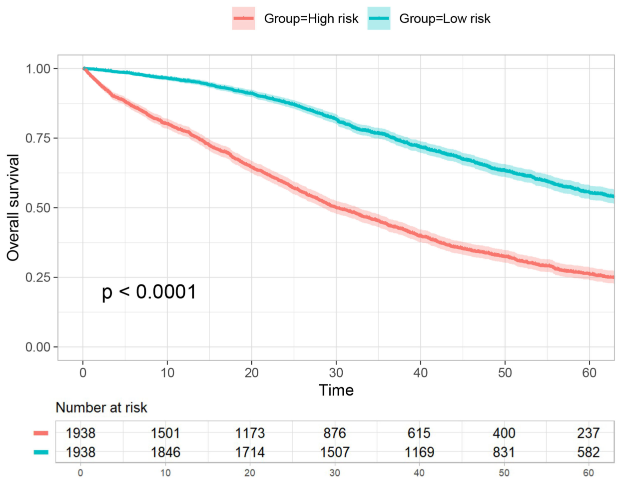

Fig. 5. OS Kaplan–Meier curve for high- or low-risk patients stratified by nomogram.

tients underwent surgery were significantly older than those that did not (35–49 years: 24.5% vs. 16.6%; ≥70 years: 18.8% vs. 27.8%, received and did not received surgery respectively, $p < 0.001$). Patients who received surgery were more likely to be white race (82.9% vs. 79.7%, received and did not received surgery respectively, $p = 0.001$) and to have private insurance (53.5% vs. 41.3%, received and did not received surgery respectively, $p < 0.001$). Moreover, patients who underwent surgery had a higher rate of poor differentiated grade (45.0% vs. 33.6%, received and did not received surgery respectively, $p < 0.001$), early AJCC T stage (T2; 42.2% vs. 36.6%, received and did not received surgery respectively, $p < 0.001$), and N stage (N0; 33.6% vs. 28.2%, received and did not received surgery respectively, $p < 0.001$). Furthermore, patients who underwent surgery were more likely to receive radiotherapy (57.4% vs. 36.3%, received and did not received surgery respectively, $p < 0.001$), chemotherapy (65.3% vs. 41.5%, received and did not received surgery respectively, $p < 0.001$), and hormone therapy (75.8% vs. 71.9%, received and did not received surgery respectively, $p < 0.001$).

Survival Analyses

Patients who underwent surgery had a longer OS compared with patients who did not (Fig. 2). Univariate and multivariate Cox regression analyses showed that surgery reduce the risk of poor OS (multivariate: HR = 0.58; 95% CI [0.54–0.62]; $p < 0.001$). Moreover, surgery enhanced OS in all subgroups, except for patients younger than 35 years old (Fig. 3).

Baseline characteristics were not statistically different between the training and validation groups (Table 2). Results of the univariate and multivariate Cox regression analyses to identify factors which are associated with OS in patients with bone-only metastasis are presented in Table 3. Multivariate analysis indicated that patients between 50–69 years old (vs age <35; HR = 1.52; 95% CI [1.16–1.98]; $p = 0.002$), black race (vs white; HR = 1.16; 95% CI [1.04–1.30]; $p = 0.009$), grade 3–4 (vs grade 1; HR = 1.54; 95% CI [1.31–1.80]; $p < 0.001$), TNBC (triple negative breast cancer) subtype (vs HR+/Her2– subtype; HR = 1.72; 95%CI [1.45–2.04]; $p < 0.001$), T3 (vs T0–1; HR = 1.19; 95% CI [1.03–1.37]; $p = 0.020$), and T4 stage (vs T0–1; HR = 1.26; 95% CI [1.10–1.43]; $p = 0.001$) had an increased risk of poor OS. On the contrary, patients with private insurance (vs uninsured; HR = 0.71; 95% CI [0.58–0.87]; $p = 0.001$), HR+/Her2+ subtype (vs HR+/Her2– subtype; HR = 0.81; 95% CI [0.71–0.93]; $p = 0.002$), HR–/Her2+ subtype (vs HR+/Her2– subtype; HR = 0.64; 95% CI [0.50–0.82]; $p < 0.001$), that received surgery (vs no surgery; HR = 0.58; 95% CI [0.53–0.64]; $p < 0.001$), chemotherapy (vs no chemotherapy; HR = 0.74; 95% CI [0.67–0.82]; $p < 0.001$), and hormone therapy (vs no hormone therapy; HR = 0.60; 95% CI [0.53–0.67]; $p < 0.001$) had a reduced risk of poor OS.

Nomogram and Stratifying Risk

For individual breast cancer patients, a total point could be calculated according to their point scale in the nomogram (Fig. 4). In this way, 1-, 3-, and 5-year survival rate was predicted clearly. For example, the clinicopathological features of randomly selected patients resulted in a total point score of 297, resulting in a 1-, 3-, and 5-year OS rate of 99.7%, 98.9%, and 98.3%, respectively. A higher score was generally associated with a worse prognosis. The Harrell's concordance index (C-index) for the nomogram to predict OS was 0.694 in the training cohort and 0.700 in the validation cohort, respectively. Moreover, plotting the calibration curves revealed good consistency between the predicted survival probability by the nomogram and the observed survival probability (**Supplementary Fig. 1**). Based on the median risk score calculated by the nomogram, patients could be discriminated in low-, and high-risk groups. Fig. 5 showed that patients with high-risk had significantly poorer OS than patients with low risk.

Discussion

Patients with MBC may benefit from locoregional surgery but evidence about it is still controversial. There is retrospective evidence with large sample size implying that MBC patients may benefit from surgical treatment. For instance, a retrospective study based on the SEER (Surveillance, Epidemiology, and End Results) database by Alexandra *et al.* [7] indicated that initial breast surgery could significantly improve survival rate of patients on stage IV of breast cancer, especially in patients with tumors smaller than 2 cm. A propensity-matched analysis by Nasreen *et al.* [17] further proved that resection of primary tumors in metastatic breast cancer improved survival. It was also reported that receiving surgical treatment, whether before or

Table 1. Clinicopathological information of breast cancer patients with distant bone metastasis.

Characteristic	Total cohort No. (%)	No surgery cohort No. (%)	Surgery cohort No. (%)	χ^2 value	*p* value
Age				144.1	<0.001
<35	282 (3.6)	129 (2.8)	153 (4.9)		
35–49	1533 (19.8)	771 (16.6)	762 (24.5)		
50–69	4062 (52.4)	2448 (52.8)	1614 (51.8)		
≥70	1874 (24.2)	1289 (27.8)	585 (18.8)		
Race				14.8	0.001
White	6279 (81.0)	3698 (79.7)	2581 (82.9)		
Black	1179 (15.2)	765 (16.5)	414 (13.3)		
Others	293 (3.8)	174 (3.8)	119 (3.8)		
Insurance status				117.2	<0.001
Uninsured	365 (4.7)	259 (5.6)	106 (3.4)		
Private	3578 (46.2)	1913 (41.3)	1665 (53.5)		
Public insurance	3808 (49.1)	2465 (53.2)	1343 (43.1)		
Grade				109.5	<0.001
1	798 (10.3)	547 (11.8)	251 (8.1)		
2	3991 (51.5)	2530 (54.6)	1461 (46.9)		
3–4	2962 (38.2)	1560 (33.6)	1402 (45.0)		
Subtype				21	<0.001
HR+/Her2–	5641 (72.8)	3460 (74.6)	2181 (70.0)		
HR+/Her2+	1202 (15.5)	683 (14.7)	519 (16.7)		
HR–/Her2+	329 (4.2)	180 (3.9)	149 (4.8)		
TNBC	579 (7.5)	314 (6.8)	365 (8.5)		
T stage				38.7	<0.001
T0–1	1256 (16.2)	746 (16.1)	510 (16.2)		
T2	3012 (38.9)	1697 (36.6)	1315 (42.2)		
T3	1402 (18.1)	841 (18.1)	561 (18.0)		
T4	2081 (26.8)	1353 (29.2)	728 (23.4)		
N stage				76.4	<0.001
N0	2351 (30.3)	1306 (28.2)	1045 (33.6)		
N1	3695 (47.7)	2398 (51.7)	1297 (41.7)		
N2	949 (12.2)	512 (11.0)	437 (14.0)		
N3	756 (9.8)	421 (9.1)	335 (10.8)		
Radiotherapy				336.1	<0.001
No	4280 (55.2)	2954 (63.7)	1326 (42.6)		
Yes	3471 (44.8)	1683 (36.3)	1788 (57.4)		
Chemotherapy				423.2	<0.001
No	3793 (48.9)	2713 (58.5)	1080 (34.7)		
Yes	3958 (51.1)	1924 (41.5)	2034 (65.3)		
Hormone therapy				14	<0.001
No	2057 (26.5)	1302 (28.1)	755 (24.2)		
Yes	5694 (73.5)	3335 (71.9)	2359 (75.8)		

Abbreviations: Her2, human epidermal growth factor receptor 2; HR, positive hormone receptors; TNBC, triple negative breast cancer.

after systemic therapy, independently increased overall survival in clinical stage IV breast cancer patients compared to systemic therapy alone [18]. Furthermore, a meta-analysis that included 216,066 patients from 42 observational studies, de novo stage IV breast cancer seem to benefit from locoregional therapy (surgery and/or localized radiotherapy) of the primary tumor [19]. However, conflicting results have been observed in prospective randomized controlled clinical trials. A study in India showed that newly diagnosed metastatic breast cancer who were sensitive to first-line chemotherapy did not improve OS of later primary site surgery patients [11]. Moreover, the latest randomized clinical trial in the topic (EA2108) indicated that although early locoregional therapy could improve locoregional control, this had no impact on breast cancer patients' survival with initial distant metastases [20]. However, a study in Turkey

Table 2. Baseline characteristics of the training and validation cohorts.

Characteristic	Training cohort No. (%)	Validation cohort No. (%)	χ^2 value	*p* value
Age			5.03	0.170
<35	145 (3.7)	137 (3.5)		
35–49	788 (20.3)	745 (19.2)		
50–69	1982 (51.2)	2080 (53.7)		
≥70	961 (24.8)	913 (23.6)		
Race			2.44	0.295
White	3131 (80.8)	3148 (81.2)		
Black	608 (15.7)	571 (14.7)		
Others	137 (3.5)	156 (4.0)		
Insurance status			0.28	0.870
Uninsured	178 (4.6)	187 (4.8)		
Private	1787 (46.1)	1791 (46.2)		
Public insurance	1911 (49.3)	1897 (49.0)		
Grade			0.06	0.972
1	396 (10.2)	402 (10.4)		
2	1996 (51.5)	1995 (51.5)		
3–4	1484 (38.3)	1478 (38.1)		
Subtype			2.51	0.474
HR+/Her2–	2805 (72.4)	2836 (73.2)		
HR+/Her2+	608 (15.7)	594 (15.3)		
HR–/Her2+	158 (4.1)	171 (4.4)		
TNBC	305 (7.9)	274 (7.1)		
T stage			3.52	0.319
T0–1	650 (16.8)	606 (15.6)		
T2	1478 (38.1)	1534 (39.6)		
T3	690 (17.8)	712 (18.4)		
T4	1058 (27.3)	1023 (26.4)		
N stage			1.75	0.625
N0	1151 (29.7)	1200 (31.0)		
N1	1871 (48.3)	1824 (47.1)		
N2	479 (12.4)	470 (12.1)		
N3	375 (9.7)	381 (9.8)		
Surgery			0.02	0.882
No	2322 (59.9)	2315 (59.7)		
Yes	1554 (40.1)	1560 (40.3)		
Radiotherapy			0.001	0.974
No	2141 (55.2)	2139 (55.2)		
Yes	1735 (44.8)	1736 (44.8)		
Chemotherapy			0.93	0.334
No	1918 (49.5)	1875 (48.4)		
Yes	1958 (50.5)	2000 (51.6)		
Hormone therapy			0.08	0.772
No	1023 (26.4)	1034 (26.7)		
Yes	2853 (73.6)	2841 (73.3)		

Abbreviations: Her2, human epidermal growth factor receptor 2; HR, positive hormone receptors; TNBC, triple negative breast cancer.

implied that surgical treatment might be beneficial for stage IV breast cancer patients [8]. We hypothesize that this may be attributable to the fact that the Turkish study included a higher proportion of patients with solitary bone-only metastases. In addition, the small sample size of prospective studies may also be associated with such conflicting results.

Considering that patients with bone metastases are in better systemic condition than those with visceral metastases, to screen out more independent and significant factors, clinicians are more likely doing surgical interventions

Table 3. OS univariate analysis of breast cancer patients with distant bone metastasis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age		<0.001		<0.001
<35	Reference		Reference	
35–49	1.11 (0.84–1.46)	0.473	1.18 (0.89–1.57)	0.239
50–69	1.65 (1.26–2.14)	<0.001	1.52 (1.16–1.98)	0.002
≥70	2.76 (2.11–3.61)	<0.001	2.16 (1.63–2.86)	<0.001
Race		<0.001		0.002
White	Reference		Reference	
Black	1.31 (1.17–1.46)	<0.001	1.16 (1.04–1.30)	0.009
Others	0.68 (0.52–0.88)	0.004	0.74 (0.56–0.97)	0.026
Insurance status		<0.001		<0.001
Uninsured	Reference		Reference	
Private insurance	0.60 (0.49–0.73)	<0.001	0.71 (0.58–0.87)	0.001
Public insurance	1.08 (0.89–1.31)	0.444	0.92 (0.95–1.13)	0.413
Grade		<0.001		0.008
1	Reference		Reference	
2	1.08 (0.92–1.25)	0.351	1.14 (0.97–1.32)	0.104
3–4	1.42 (1.22–1.66)	<0.001	1.54 (1.31–1.80)	<0.001
Subtype		<0.001		<0.001
HR+/Her2–	Reference		Reference	
HR+/Her2+	0.79 (0.70–0.90)	<0.001	0.81 (0.71–0.93)	0.002
HR–/Her2+	0.85 (0.68–1.06)	0.157	0.64 (0.50–0.82)	<0.001
TNBC	2.65 (2.32–3.03)	<0.001	1.72 (1.45–2.04)	<0.001
T stage		<0.001		0.001
T0–1	Reference		Reference	
T2	0.96 (0.85–1.09)	0.563	1.06 (0.94–1.21)	0.344
T3	1.12 (0.97–1.30)	0.117	1.19 (1.03–1.37)	0.020
T4	1.37 (1.21–1.56)	<0.001	1.26 (1.10–1.43)	0.001
N stage		0.144		
N0	Reference		NA	
N1	1.08 (0.98–1.19)	0.146		
N2	1.07 (0.93–1.23)	0.364		
N3	1.19 (1.02–1.38)	0.024		
Surgery				
No	Reference		Reference	
Yes	0.53 (0.48–0.58)	<0.001	0.58 (0.53–0.64)	<0.001
Radiotherapy				
No	Reference		Reference	
Yes	0.78 (0.71–0.84)	<0.001	0.98 (0.90–1.07)	0.681
Chemotherapy				
No	Reference		Reference	
Yes	0.70 (0.64–0.76)	<0.001	0.74 (0.67–0.82)	<0.001
Hormone therapy				
No	Reference		Reference	
Yes	0.58 (0.53–0.63)	<0.001	0.60 (0.53–0.67)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

in these patients. Hence, it is meaningful to evaluate the survival benefit of surgery and identify independent prognostic factors toward breast cancer patients with bone-only metastasis. Here, a large cohort of breast cancer patients, from the NCDB database, with bone-only metastasis, from 2010 to 2015, was analyzed. The Kaplan–Meier survival analysis showed that patients who underwent surgery had an improved OS compared to patients who did not. This survival benefit was still significant in multivariate Cox regression analysis, indicating that receiving surgery was an independent prognostic factor for de novo stage IV breast cancer. Further subgroup analysis showed that surgery was beneficial in all subgroups, except for patients younger than 35 years old. This might be due to the small sample size (282) of young patients. After randomly dividing all patients into a training cohort and a validation cohort, independent OS prognostic factors were assessed using a multivariate Cox regression model. As a result, several independent prognostic factors were identified, including age, race, insurance status, grade, subtype, T stage, surgery, chemotherapy, and hormone therapy. It is well known that nomograms are useful to inform clinical decision making as well as predicting patient prognosis [21]. Hence, a prognostic nomogram was created including independent prognostic factors identified in the multivariate Cox regression analysis. The nomogram could discriminate patients into high-risk and low-risk groups, which could help surgeons make appropriate treatment decisions. Among the raining and validation set, the nomogram exhibited an acceptable predictive capability with a C-index around 0.7, which was comparable to many well-recommended nomograms [22,23].

The large sample size, 7751 patients with solitary bone-only metastasis is the strengths of this study. However, this study has different limitations. Detailed information, such as extent of bone metastasis (bone oligometastasis or multifocal metastasis), residues of tumor resection (R0, R1, or R2), concomitant disease, are not available in NCDB database. They might be confounding factors associated with surgeon's treatment decisions. Moreover, the surgery procedure was not described in detail in our study, which is a point of debate when clinicians plan the surgical treatment for patients with distant metastases. In addition, selection bias is inherent in retrospective studies, and therefore, more prospective investigations with large sample size are needed to validate our results.

Conclusions

The findings of this study suggest that surgery may improve OS in patients with bone-only metastatic breast cancer. Additionally, the nomogram created in this study showed an acceptable capacity to individually predict long-term survival of patients with de nova bone-only metastatic breast cancer.

Availability of Data and Materials

The data generated and/or analysed during the current study are available in the NCDB database (https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/).

Author Contributions

ZW and SZ—designed the research study; ZW, SZ, DQ, RW—analyzed the data; ZW and SZ—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202335174.8.

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